

Production of Levulinic Acid and Use as a Platform Chemical for Derived Products

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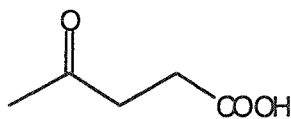
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ABSTRACT

Levulinic acid (LA) can be produced cost effectively and in high yield from renewable feedstocks in a new industrial process. The technology is being demonstrated on a one ton/day scale at a facility in South Glens Falls, New York. Low cost LA can be used as a platform chemical for the production of a wide range of value-added products. This research has demonstrated that LA can be converted to methyltetrahydrofuran (MTHF), a solvent and fuel extender. MTHF is produced in >80% molar yield via a single stage catalytic hydrogenation process. A new preparation of δ -aminolevulinic acid (DALA), a broad spectrum herbicide, from LA has also been developed. Each step in this new process proceeds in high (>80%) yield and affords DALA (as the hydrochloride salt) in greater than 90% purity, giving a process that could be commercially viable. LA is also being investigated as a starting material for the production of diphenolic acid (DPA), a direct replacement for bisphenol A.

Introduction

Biomass can be used as a raw material to produce large numbers of chemicals, each with the potential to be as fundamental to the chemical industry as methane or BTX. Yet, to date, many of these products have failed in the marketplace because they do not pass the most practical test of market viability: *is the product available at a low enough cost to use as a chemical product or intermediate?* Levulinic acid (**1**, LA, 4-oxopentanoic acid), has frequently been proposed as such a building block. (Thomas & Barile 1984; Kitano, Tanimoto & Okabayashi 1975).



1, levulinic acid

Despite its status as an expensive and relatively small market specialty chemical (about 1 million lb/year at \$4.00 - \$6.00/lb), LA and its derivatives have found use in highly diverse areas. Some of these applications are summarized in Table 1.¹

Table 1 - Selected Levulinic Acid Applications

<u>Application</u>	<u>Reference</u>
Chiral reagents	Meyers et al. 1998
Biologically active materials	Bitonti et al. 1995
Polyhydroxyalkanoates	Jang & Rogers 1996
Polymers	van Aert et al. 1997; Taylor, Kielmeyer and Golino 1995
Polymerization initiators	Lai 1991
Antifouling compounds	Bush 1999
Personal care products	Tsucha 1994
Lubricants	Adams et al. 1998
Adsorbents	Raidel & Aschenbrenner 1998
Printing/Inks	Gundlach 1998
Coatings	Nakazato & Konishi 1995
Electronics	Oono et al. 1996
Photography	Shimizu et al. 1996
Batteries	Maekawa & Miyaki 1997
Drug delivery	Hille 1996
Corrosion inhibitors	Armstrong & Phillips 1993

The preparation of LA is not difficult, and a number of approaches have been reported for its synthesis. The most widely used approach is the dehydrative treatment of biomass or carbohydrates with acid (Lourvanij & Rorrer 1994; Jow et al. 1987; Dahlmann 1968; Farone & Cuzens 1998). LA has also been produced by hydrolysis of acetyl succinate esters (Farnleitner et al. 1991), by acid hydrolysis of furfuryl alcohol (Itaya et al. 1988), by oxidation of ketones with ozone (Edwards 1986) or with Mn(OAc)₃ (Vaerman & Bertrand 1972). LA has been produced by Pd-catalyzed carbonylation of ketones (Cavinato & Toniolo 1990) and by alkylation of nitroalkanes (Ballini & Petrini 1986). However, these methods frequently form large amounts of side products and intractable materials, or require expensive starting feedstocks.

Recently, a new process developed by Biofine Corporation eliminated many of the existing problems with LA production. The Biofine process uses acid hydrolysis of 6-carbon sugars as the key step for LA production, and minimizes side product formation and the resulting separation problems by significantly improving the traditional engineering of the LA production process through a novel, two reactor system (**Figure 1**). (Fitzpatrick 1997, 1990).

¹The applications cited in Table 1 and subsequent tables are illustrative but not exhaustive. Many additional examples exist in the patent and open literature. In each case, LA or its derivatives are listed as useable in the given application, but may not be the primary focus of the citation.

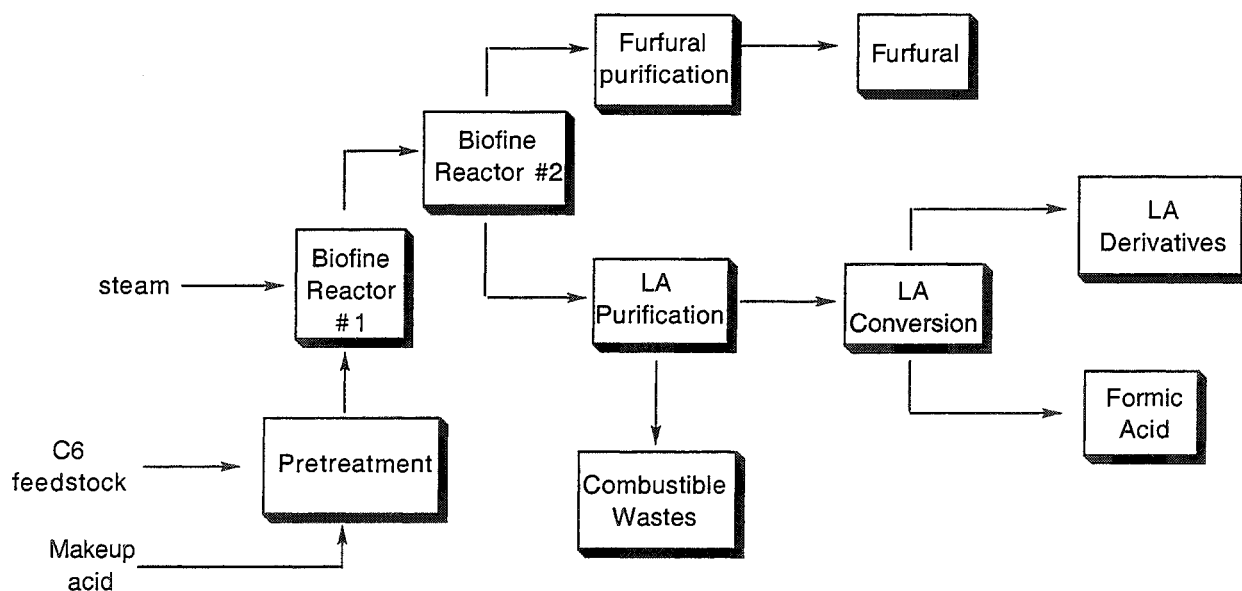


Figure 1: The Biofine Process

The process supplies carbohydrate containing materials to a first reactor where they are hydrolyzed at 210-230°C for 13-25 seconds in the presence of 1-5% mineral acid. This initial hydrolysis produces hydroxymethylfurfural, which is removed continuously and supplied to a second reactor. In the second reactor, the hydroxymethylfurfural is hydrolyzed further at 195-215°C for 15-30 minutes to produce LA, which is again continuously removed. The LA yield is $\geq 60\%$, based on the hexose content of the carbohydrate-containing starting material, one of the highest reported in the literature. The result is a cost effective production of LA, making it suitable as a starting material for a wide variety of products. The technology can be successfully employed using diverse cellulose-containing waste materials such as paper mill sludge, urban waste paper, agricultural residues and cellulose fines from papermaking as starting materials. Economic projections indicate that the LA production cost could fall as low as \$0.04 - \$0.10/lb depending on the scale of the operation. Furthermore, the impact on waste reduction and domestic energy use is large. Department of Energy metrics project energy savings of 75.6 trillion Btu/yr and waste reduction of 26.2 million tons/yr by 2020. Biofine is operating a 1 ton/day pilot plant facility in South Glens Falls, New York to demonstrate the ability to scale this process to an industrially useful size.²

Typically, however, a biomass derived material must pass a second test: *what can the material be used for and is there a market?* To address this issue, a research consortium was established in 1996. The consortium brought together two industrial partners, Biofine and Chemical Industry Services with the National Renewable Energy Laboratory (NREL), the Pacific Northwest National Laboratory (PNNL), and the New York State Energy Research and Development Authority (NYSERDA). This consortium has been developing technology to convert LA into a larger suite of chemical products. Laboratory research has studied three products: methyltetrahydrofuran (MTHF), a fuel additive with a huge potential market, δ -amino levulinic acid (DALA) a broad spectrum herbicide/pesticide with a projected market of 200 - 400 million

² Projections are based on MTHF as a fuel oxygenate, addressing a potential market of 8 billion lb/yr.

pounds/year, and diphenolic acid (DPA), a substitute for bisphenol A in polymer manufacture. These products have the potential to expand the market need for LA into the hundreds of millions of pounds. Table 2 summarizes possible market demand for LA from a group of LA derivatives. In the past, LA has been investigated as a starting material for several of these materials, however, its traditionally high cost has prevented widespread use of known technology (MTHF: Hachihama & Imoto 1942; Hayashi, Negoro & Hachihama 1954; Helberger, Ulubay & Civelekoglu 1949; DALA: Benedikt & Kost 1986; DPA: Bader 1960). The combination of a low cost source of LA with new technology has opened up new opportunities for LA as a chemical feedstock.

Table 2 - Products from LA and Potential LA Markets Demand

<u>Product</u>	<u>Use</u>	Potential LA Market (million <u>lb/yr</u>)
MTHF	fuel extender	10000 - 100000
DALA	biodegradable herbicide	175 - 350
Diphenolic acid	monomer	35
THF	solvent	200
BDO	monomers	200

Results - New Approaches to Derivatives of Levulinic Acid

Methyltetrahydrofuran

Large scale use of LA has recently been linked to automobile fuel extenders, such as MTHF. It is miscible with gasoline at all proportions and has favorable oxygenate and vapor pressure properties (Thomas and Barile 1984). Since the U. S. uses about 100 billion gallons of gasoline/yr, replacement of as little as 1% (similar in volume to the usage of ethanol in gasohol) would result in a yearly demand of 1 billion gallons of MTHF, equivalent to over 10 billion pounds of LA. Early work in the 1980s (Thomas & Barile 1984; Rudolph and Thomas, 1988) investigated the use of two LA derivatives, MTHF and angelicalactone (AL), as fuel blending agents. Direct conversion of LA to MTHF is reported to occur in only low yield (Christian, Brown & Hixon 1947). However, several indirect LA processing routes are reported that lead to MTHF (Figure 2).

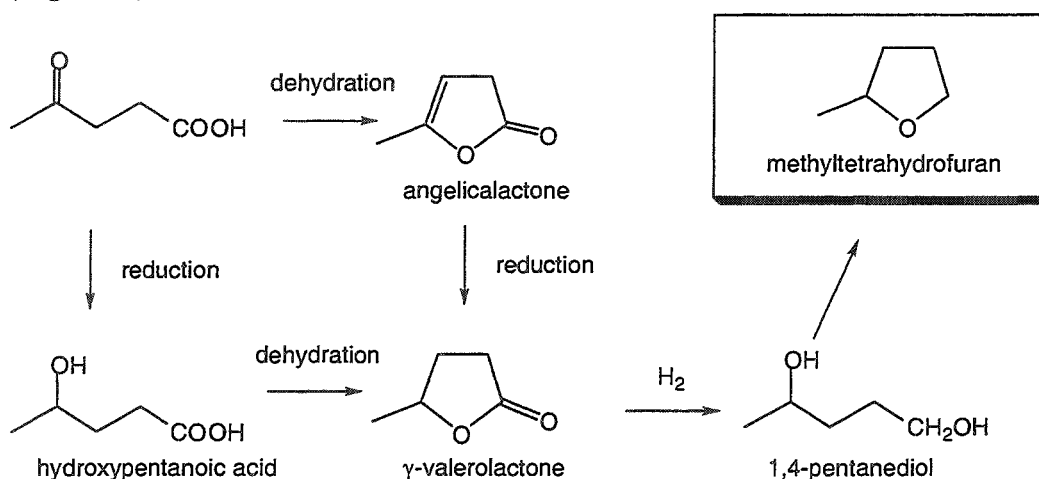


Figure 2 - Conversion of LA to MTHF

An intermediate central to LA based MTHF processes is γ -valerolactone (GVL). This material can be prepared by several different routes. Simple heating of LA to about 160°C in the presence of acid gives a high yield of AL (Thomas and Barile 1984; Leonard 1957). A subsequent reduction step converts AL to GVL, and then to 1,4-pentanediol (PDO). PDO is readily dehydrated to MTHF (Olah, Fung & Malhotra 1981) upon heating in the presence of acid. Alternatively, LA can also be reduced to 4-hydroxypentanoic acid (HPA). This material can undergo cyclization to GVL and conversion to MTHF, again via PDO.

The conversion of LA to GVL has been investigated by several groups. Schutte and Thomas (Schutte and Thomas 1930) hydrogenated LA using a platinum oxide catalyst to give GVL in 87% yield. LA was hydrogenated to GVL in the neat liquid phase with a Raney nickel catalyst in 94% yield (Kyrides, Groves & Craver 1945; Christian, Brown & Hixon 1947). Changing to a copper-chromite catalyst produced a complex mixture of GVL, PDO and MTHF. This is the first report of MTHF as a byproduct, although its ready formation from PDO by thermal decomposition/dehydration explains its presence. Rhenium catalysts (Re black, Re(IV) oxide hydrate) for hydrogenation of LA to GVL have also been described (Broadbent et al. 1959). The subsequent reduction of GVL to PDO has also been studied. Hydrogenation of GVL over copper-chromite catalyst gave 79% PDO (Folkers and Adkins 1932). In a later study up to 83% yield of PDO was achieved. At higher reaction temperatures, PDO yields dropped and MTHF was found in a low-boiling fraction (Christian, Brown & Hixon 1947).

More recent studies have focused on homogeneous catalysis of the hydrogenation steps. Both ruthenium (Joó, Toth & Beck 1977) and rhodium (Joó, Somsák & Beck 1984) complexes catalyze hydrogenation of LA at low temperature (60°C) in aqueous solutions. GVL is also produced from LA in 85-100% yield using ruthenium iodocarbonyl complexes (Bracca, Raspolli-Galletti & Sbrana 1991). Ruthenium triphenylphosphine complexes give 99% conversion and 86% yield of GVL in toluene solution (Osakada, Ikariya & Yoshikawa 1982).

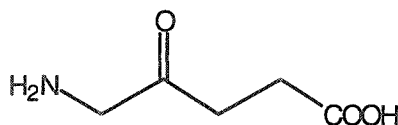
The major projected use of MTHF is as a transportation fuel extender. Because it is miscible with gasoline at all proportions and hydrophobic, MTHF could be blended at the refinery and transported by pipeline. In contrast, ethanol must be added later in the distribution process because contamination with water can cause phase separation. MTHF can be blended in gasoline up to 60% by volume without adverse engine performance (Lucas et al., 1993). MTHF has a higher specific gravity than gasoline; therefore, mileage from MTHF blended fuel would not decrease. As a component of "P-series" fuels (recently approved by the Department of Energy), MTHF can be used to meet the requirements for alternative fuel fleet vehicles stipulated by the Energy Policy Act of 1992. The "P-series" fuels are blended such that they have a minimum antiknock index of 87 and a maximum vapor pressure of 15 psi. P-series fuel emissions are generally below those for reformulated gasoline using methyltertiarybutyl ether (MTBE) and are well below federal emissions standards.

Work carried out at PNNL has built upon the background chemical research in LA reactions. Batch reactor tests were performed to screen a series of catalyst formulations and processing conditions for use in hydrogenating levulinic acid. Initial tests in dilute phase with 1,4-dioxane solvent have provided the basis of continuous-flow reactor tests with the Biofine LA product from their demonstration plant. Laboratory-scale work has shown the conversion of LA into MTHF with a single-bed catalytic hydrogenation process that uses a catalyst consisting of palladium and rhenium metals on carbon at elevated temperature and pressure. The LA undergoes multiple hydrogenations (three moles of hydrogen per mole of LA) and two

dehydrations in a single reaction step. PNNL was recently issued a patent for the catalyst composition and the operating parameters (Elliott and Frye 1999). Operating conditions are 240°C and 1500 psig using liquid hourly space velocities around 1 liter of LA/liter of catalyst bed/hour. Lab tests have indicated an 83% yield on a theoretical (molar) basis. On a weight basis, the yield is 63 pounds of MTHF for every 100 pounds of LA. Literature values using competing processes give low yields (3%) of MTHF as a minor by-product. Efforts are under way to scaleup production of MTHF from LA in a mobile processing unit at Biofine's demonstration plant. MTHF production is projected at about 20 gallons per day.

Delta-aminolevulinic acid (DALA)

DALA (2) is a broad spectrum, biodegradable herbicide that shows high activity toward dicotyledonous weeds while showing little activity toward monocotyledonous crops such as corn, wheat, or barley. DALA is completely biodegradable with a broad spectrum of activity rivaling and possibly exceeding that of Monsanto's Roundup®. DALA exerts its effects by stimulating overproduction of tetrapyrroles in the plant at night. In daylight, the accumulated tetrapyrroles photosensitize the formation of singlet oxygen in the plant, leading to its death (Rebeiz et al 1984; Rebeiz et al. 1994). More recently, DALA has been found to be useful as an insecticide (Rebeiz, Juvik & Rebeiz 1988) and as a component in photodynamic therapy as a cancer treatment (Rebeiz et al. 1996).



2, DALA

A variety of synthetic routes for DALA have been reported. DALA can be prepared from N-substituted amino acids (Wang & Scott 1997), and through stepwise buildup of the carbon chain (Appleton et al. 1998). More elegant strategies used cyclic starting materials such as furfurylamine (Kawakami, Ebata & Matsushita 1991), 5-hydroxy-2-pyridone (Herdeis & Dimmerling 1984), N-methoxycarbonyl-3-piperidinones (Matsumura, Takeshima & Okita 1994), and 5-hydroxymethyl-2-furfural (Cottier et al. 1995). The biological activity of DALA has also led to a search for processes that can be applied at commercial scales. A number of DALA production patents have been issued (Aronova et al. 1974; Kawakami et al. 1994; Descotes et al 1994; Takeya, Shimizu & Ueki 1995).

The obvious starting material for the preparation of DALA is LA, which requires formation of a C-N bond at the C5 carbon. Several amination methods have been successful on laboratory scale, but none of them have been scaled up to commercial levels. The most common approach for activating the C5 position toward amination is bromination of LA in an alcohol medium (MacDonald 1974) to give mixtures of 5-bromo- and 3-bromoesters that are separated by distillation. The 5-bromolevulinate is aminated using nucleophilic nitrogen species such as sodium azide (Ha et al. 1994). These various steps are combined to give the conventional DALA synthesis shown in Figure 3 (Benedikt & Köst 1986). LA (1) is brominated to give 5-bromolevulinic acid 3. To introduce the key amino group, 3 is treated with potassium phthalimide, giving intermediate 4. Acid hydrolysis of 4 gives DALA. The major difficulties with this approach are the relatively low yields in the first two steps and the generation of a large amount of a waste product, 5. Introduction of the amino group into DALA is highly inefficient because only a single atom from the potassium phthalimide is used. The remainder of the

structure is waste. More generally, none of the reported approaches are suitable for large scale manufacture of DALA because of the need for multistep syntheses, expensive starting materials, or toxic intermediates.

The key areas of study at NREL for DALA manufacture have been the improvement of each of these synthesis steps with particular focus on overall cost effectiveness. The NREL work has significantly improved the yield of the first two steps and the efficiency of the second (Figure 4).

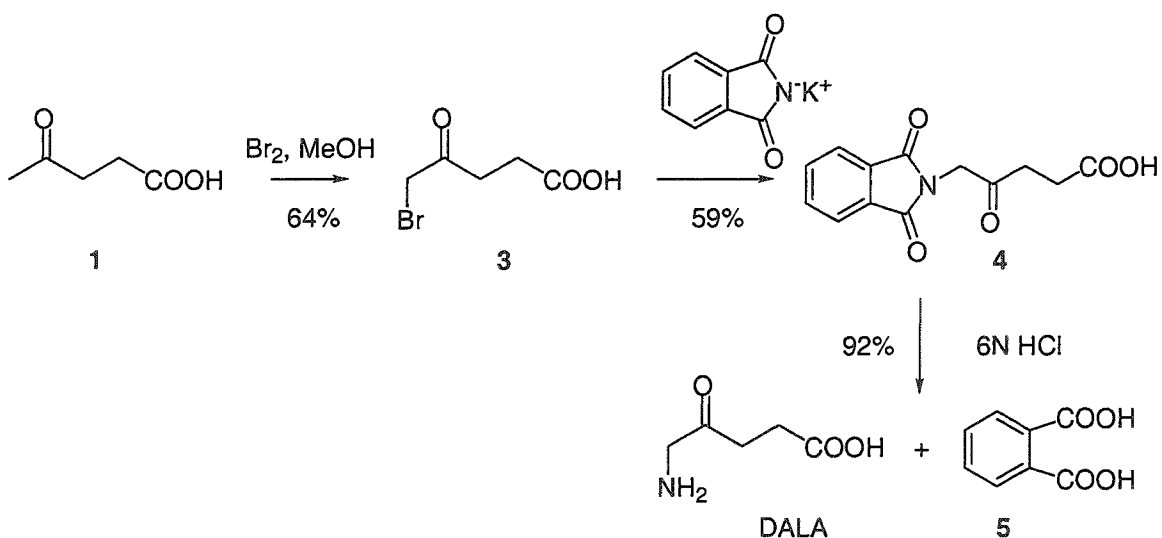


Figure 3 - Conventional Synthesis of DALA

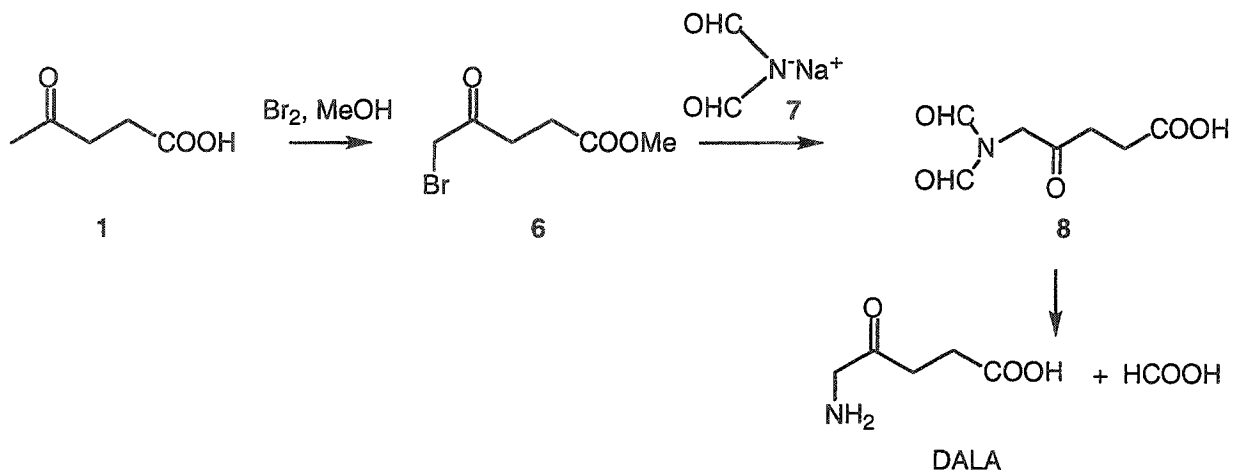


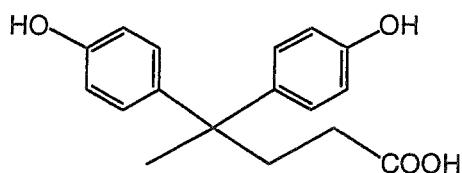
Figure 4 - NREL Synthesis of DALA

The NREL synthesis also begins with LA, which is brominated in MeOH to give methyl 5-bromolevulinate 6. This ester is treated with diformylamide anion 7 (easily prepared from NaOMe and formamide (Yinglin and Hongwen 1990)) to give 8. Acid hydrolysis of this intermediate leads to DALA. The only side product observed from the hydrolysis is formic acid. Each of the steps proceeds in high (>80%) yield and affords DALA (as the hydrochloride salt) in

greater than 90% purity, giving a process that could be commercially viable.³ The material prepared by this process has been submitted for herbicide testing at the University of Illinois. The first samples were 85% as effective as a control sample of DALA. More recently, the process has been improved further by use of a different amination reagent for the second step of the process. This new reagent generates much less waste, and can be used in several solvents.

Diphenolic acid

Diphenolic acid (9) is a material that has found wide application in the production of polymers and other materials.



9, diphenolic acid

The material is easily prepared from the reaction of LA with two moles of phenol (Isoda & Azuma 1996). DPA can serve in many of the same applications as bisphenol A (BPA), but the lower cost of the latter has reduced the DPA market. Since the Biofine process offers LA at a much lower cost, it is reasonable to again consider DPA as a renewables based polymer precursor. Work has started at RPI on near term applications for DPA, particularly ones that displace currently marketed BPA products. Researchers are exploring DPA/BPA copolycarbonate and copolyarylate combinations that could partially or wholly displace BPA formulations. Within these combinations, researchers are also studying the use of dibrominated DPA in fire retardants. Brominated DPA also has some promise as an environmentally acceptable marine coating that could replace the toxic tributyltin. Further development of DPA uses will concentrate on highly crosslinked polymers and charged polyesters, or "ionomers."

Market penetration of Biofine's DPA has near term potential; DPA has been produced commercially for many years by reacting LA with phenol. LA's price is the most important component of DPA's price, which is currently around \$3/lb. If LA were produced for \$1/lb, DPA could likely be produced for \$1.20/lb. The market for BPA is estimated to be over 500 million lb/yr. A \$1.20/lb DPA might not only capture 20% of this market, but also recapture some 5 million lb/yr of its old use as a coating material. DPA may even perform better in some applications. The goal is to achieve a DPA market size of 15 million lb/yr over the next five years, creating a 7 million lb/yr market for LA.

DPA's widest use is as a component in polymers, however, it has also found applications in several other areas. Applications are summarized in **Table 3**.

³A process patent was allowed on the NREL DALA approach in late 1998. At this writing, we are awaiting its issuance.

Table 3 - Selected Diphenolic Acid Applications

<u>Application</u>	<u>Reference</u>
Thermoplastics	Weber & Weiser-Elbl
Polysulfones	Weber & Heckmann 1998
Polyphenylene ethers	Tagle et al. 1997
Hyperbranched and dendrimeric polyesters	Chu et al. 1997
Thermally reversible isocyanates	Markle, Brusky and Cremeans
Phenolic and polyester resins	Demmer & Irving
Polycarbonates	Hoogebom
Heat sensitive recording media	Kurisu, Motosugi & Kobayashi
Electronics	Watanabe, Kukemura, & Nakura
Printing/Inks	Malhotra et al
Fragrances	Anderson, Frater & Gyax
Medicinals	Brooks et al.
Dyes/Pigments	Ogawa et al.
Lubricants	Chafetz et al.
Fire retardant materials	Rosenquist
Polymeric coatings	Blegen
Adhesives	Taira et al.
Paints	Homen & Olander

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